## REMARKS

**The Amendments**

The title and abstract are amended to address the objection thereto in the Office action.

The claims are amended in a merely formal, non-substantive manner for consistency. The amendments do not narrow the scope of the claims and/or were not made for reasons related to patentability. The amendments should not be interpreted as acquiescence to any objection or rejection made in this application.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

**The Restriction Requirement**

The Final status of the Restriction requirement is noted. Applicants submit that the non-elected method of making and method of use claims would be subject to rejoinder upon allowance of the elected compound/composition claims. Thus, the method claims are retained in the application. It is not necessary to cancel the non-elected claims in this circumstance. The claims have been amended to better conform to US practice.

**The Objections to the Title and Abstract**

The objections to the title and abstract are believed to be addressed by the above amendments.

**The Claim Objections**

The objections to claims 2-6 and 9 are rendered moot by the above amendments.

**The Rejection under 35 U.S.C. §112, first paragraph**

The rejection of claims 1-6 and 9 under 35 U.S.C. §112, first paragraph, for alleged lack of enablement, is respectfully traversed.

The rejection is made based on the allegation that the specification does not enable one of ordinary skill in the art to make and use the solvates or solvates of salts of the compounds as claimed. The rejection is based on an analysis of the Wands factors and

applicants address these factors below. However, applicants urge that there are other threshold issues to consider before the Wands factors.

Although the Examiner is certainly aware of this, applicants reiterate that adequate enablement of a claim is not viewed merely by what is in applicants' specification. The knowledge of those of ordinary skill in the art must also be considered; see, e.g., DeGeorge v. Bernier, 768 F.2d 1318, 226 USPQ 758 (Fed. Cir. 1985). See also, Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524, 1534, 3 USPQ2d 1737, 1743 (Fed. Cir. 1987), stating: "a patent need not teach, and preferably omits, what is well known in the art." The position taken in the Office action is that formation of solvates requires undue experimentation and is unpredictable. Applicants believe that this conclusion was arrived at because the wrong question is being considered. The conclusion in the Office action appears to be based on the question of whether it is routine or predictable – without conducting any experimentation – to determine whether a specific solvent will form a solvate with a specific compound and what the nature of such solvate would be. The correct question should be: Can one of ordinary skill in the art conduct routine experimentation to provide solvates of the claimed compounds which would be useful for carrying out the invention and can one of ordinary skill in the art routinely determine the nature of any such solvates? Applicants submit that this latter question is the proper one because the law is clear that adequate enablement can be provided from the knowledge available in the art and can be provided from one of ordinary skill in the art conducting routine experimentation. Under this correct standard, there is adequate enablement for one of ordinary skill in the art to make and use solvates as recited in the instant claims.

One of ordinary skill in the pharmaceutical compounds art is well aware:

- of the definition of solvates and the chemical formula of any theoretically possible solvate or hydrate for a given compound;
- that is conventional to provide solvates of chemical compounds;
- that only routine experimentation in this field is needed to determine what, if any, solvates of a given compound can be provided; and
- of solvents, including water, which are commonly used to provide solvates (including hydrates which are solvates with water as the solvent) of compounds intended for use in pharmaceutical applications.

Thus, determining what solvates for the specific claimed compounds could be practically obtained and whether they are suitable for use in pharmaceutical applications involves only routine experimentation in this field.

As additional proof that determining suitable solvates would be routine, applicants refer to the *Vippagunta* article cited in the Office action to support the rejection and a further article by *Hilfiker*, filed herewith.

The *Vippagunta* article cited in the Office action does not support that one of ordinary skill in the art could not make and use solvates of a particular compound. *Vippagunta* may support the notion that one of ordinary skill in the art cannot accurately predict – beforehand – whether a particular compound will form a solvate with a particular solvent or what the nature of the resulting solvate would be. But, as discussed above, this is not the proper inquiry. The article supports that only routine experimentation by one of ordinary skill in the art is needed to identify, prepare and characterize suitable solvates of a given compound. For example, *Vippagunta* on page 15, top of first column, states:

> It has been established that approximately one-third of the pharmaceutically active substances are capable of forming crystalline hydrates. (hydrates being a type of solvate, Emphasis added.)

Likewise, the abstract of *Vippagunta* starts with the statement:

> Many drugs exist in the crystalline solid state due to reasons of stability and ease of handling … Crystalline solids can exist in the form of polymorphs, solvates or hydrates. (Emphasis added.)

Also on page 4, first paragraph, *Vippagunta* states:

> Most organic and inorganic compounds of pharmaceutical relevance can exist in one or more crystalline forms. … The common crystalline forms found for a given drug substance are polymorphs and solvates. (Emphasis added.)

Moreover, *Vippagunta* teaches various solvates, structural aspects thereof, examples thereof, including preparation techniques and techniques for the characterization thereof, throughout its disclosure; see, e.g., pages 15-18. *Vippagunta* thus demonstrates that one of ordinary skill in the art in the field of pharmaceuticals would know how to proceed in preparing solvates and how such solvates would be identified or characterized, e.g., by polarized light microscopy, etc. See the extensive list of techniques identified on column 2 of page 18 of

*Vippagunta*. While some experimentation would be required, such would just be routine to those of ordinary skill in the art. Further, it would be routine in the art to determine whether or not solvates are possible for any specific compound. While predicting what solvates could be formed before doing any experimentation may be difficult, the formation of solvates is common with pharmaceutically active ingredients and methods of providing and characterizing them are well-known and widely applied routinely. In sum, *Vippagunta*, rather than supporting a lack of enablement rejection, supports the opposite, i.e., that determining and providing solvates of the compounds, as recited in the claims, would be well within the ordinary skill in the art with routine experimentation.

Additionally, applicants cite and provide herewith the *Hilfiker* reference (J.Therm.Anal.Cal., vol. 73 (2003), pp. 429-440). This article reflects the state of the art contemporaneous with the time of applicants' invention. The article recognizes the importance in the pharmaceutical industry of polymorphism and solvates. *Hilfiker* states (page 429): "Frequently it is quoted that about half of all small organic molecules can exist as polymorphs or solvates. In our experience this number is closer to 80%." *Hilfiker* (page 430) recognizes that it was known to perform polymorphism screening to "reveal all relevant polymorphic forms" and that a number of methods were known for characterizing the resulting polymorphs, e.g., "differential scanning calorimetry (DSC), x-ray diffraction (XRD), Raman spectroscopy, etc. *Hilfiker* (pages 430-431) discusses that the process of finding and characterizing the polymorphs, hydrates and solvates, involves a number of steps which were known in the art. But *Hilfiker* points out (page 431) that high-throughput screening techniques were available to perform such steps more quickly with less resources. It also describes (pages 430-431) techniques by which multiple, miniaturized experiments can be simultaneously conducted to determine solvates for a compound.

Thus, one of ordinary skill in the art is well aware that solvate formation is a very common phenomenon associated with drug substances and that the generation and examination of solvates can be conducted using highly automated techniques. In view thereof, the allegation that undue experimentation would be needed by one of ordinary skill in the art to provide solvates of the claimed compounds is refuted on the record. In fact, such experimentation is clearly routine in the pharmaceutical field.

Taking consideration of all of the above points, applicants assess the Wands factors and the comments thereon in the Office action as follows.

The Nature of the Invention – As stated in the Office action, the invention encompasses solvates and solvates of the salts of the compounds of formula (I) and there is no further description of the specific solvates in the disclosure. But such does not support any conclusion that the invention is not enabled. As fully discussed above, since providing solvates would be routine to one of ordinary skill in the art, describing the specific solvates is unnecessary for one of ordinary skill in the art to carry out the claimed invention.

The State of the Prior Art and the Level of Unpredictability in the Art – This is discussed in detail above. Applicants also take note of the fact that the claims in a large number of more recently issued patents directed to compounds in the pharmaceutical field include the recitation of solvates and/or hydrates therein without specifically describing preparation of them in the specification. Even a small sampling of recently issued US patents exemplifies this, i.e., U.S. Patent Nos. 7,351,841; 7,321,059; 7,320,995; 7,432,272; 7,345,806; each recite solvates of the compounds in their claims. This further evidences the conventional nature in the pharmaceutical art to make and use solvates (which include hydrates) of the base compounds. Again, applicants urge that, when the correct question is considered, making and using the invention is not unpredictable for one of ordinary skill in the art when using experimentation which is routine in the art. In any event, that there is some unpredictability and that some experimentation may be needed do not negate a finding of adequate enablement. The standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).

The Amount of Direction Provided and the Existence of Working Examples – The Office action further alleges that the specification provides no direction or guidance on how to make the solvates encompassed by the invention. However, as shown above, it was routine for one of ordinary skill in the art to make solvates. As stated above, "a patent need not teach, and preferably omits, what is well known in the art." Spectra-Physics. Further, it is well established that no working examples are required to establish enablement; see, e.g., In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and, In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). Particularly in cases like the present, where the allegedly un-exemplified subject matter is a routinely provided derivative of the compounds for which working examples are provided, the presence or absence of working examples would be of minimal relevance in determining enablement. The Office action admits that the base compounds are enabled and examples for their preparation are provided. These base

compounds and their pharmaceutical activity is the main characterizing feature of the invention. From this disclosure, one of ordinary skill in the art in the pharmaceutical arts would immediately consider the use of the solvates of these base compounds and their salts and the application clearly describes that solvates of these compounds are also included in the invention. One of ordinary skill in the art can then readily conduct routine experiments using conventional methods – and even automated methods – to determine the useful solvates of these compounds. As a result, applicants fail to see how one of ordinary skill in the art would not be able to practice the invention as claimed. It is not necessary for applicants to exemplify formation of a solvate to enable such a routine derivative of the exemplified base compounds.

The Breadth of the Claims – The breadth of the claims is not unreasonable. The claims are directed to compounds of the formula (I) and the salts, solvates and solvates of salts thereof. Formula (I) is quite well specified with only two variables which are reasonably well specified also. The fact that solvates are included does not make the scope of the claims broad. From all of the above evidence, including that relied on to support the rejection, one can only conclude that there would be limited number of solvates and one of ordinary skill in the art can routinely determine what they are. Applicants additionally point to the excerpt from *Guillory et al.* ("Generation of Polymorphs, Hydrates, Solvates and Amorphous Solids," pp. 202-208) provided herewith. The excerpt, see particularly page 206, confirms that one of ordinary skill in the art would look to a small set of solvents (particularly water to form a hydrate) which are most well known for forming solvates of compounds.

The Quantity of Experimentation Needed and the Level of One of Ordinary Skill in the Art – Applicants respectfully disagree that assessing the compounds for providing solvates requires undue experimentation. The *Hilfiker* reference cited above makes clear that high-throughput automated methods were available for determining solvates. Further, the requirement for some experimentation – even a large amount – does not equate to **undue** experimentation or lack of enablement. Where the experimentation required is merely routine experimentation to one of ordinary skill in the art, it is not undue experimentation and does not support a case for lack of enablement. See, e.g., Wands, at 8 USPQ2d 1404, stating: "Enablement is not precluded by the necessity for some experimentation ... . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation'." See also Ex parte Jackson, 217 USPQ 804 (Bd. Pat. App. 1982), stating: "The determination of what constitutes undue experimentation in a

given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed." The conventionality in the art of providing solvates makes their provision routine, rather than undue, regardless of the amount of experimentation needed. Further, the Office action admits that the level of skill in the art is high, which further supports enablement. The level of skill in this art would generally be that of a Ph.D. organic chemist, who would be more than adequately trained to conduct or direct the routine experimentation needed to prepare the claimed solvates.

Considered as a whole, applicants urge that the Wands factors clearly support that the claims are reasonably enabled.

As a further basis for traversal of the rejection, applicants urge that, before even considering the Wands factors, a threshold burden lies with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims to support a rejection under 35 U.S.C. §112, first paragraph, for lack of enablement. See, e.g., MPEP §2164.04 citing In re Marzocchi et al., 169 USPQ 367 (CCPA 1971), which states:

> ".. a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein..",

and further,

> "..it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." (emphasis original).

In the instant case, the specification's disclosure corresponds in scope with the claims since its general description of making and using the invention applies to the full scope of claimed compounds, which the disclosure makes clear (see, e.g., page 4, line 20; and page 14, lines 9-10) includes the solvates and solvates of salts thereof. The Office action fails to provide any

allegation that the truth or accuracy of the inventors' disclosure is doubted. Nor has any convincing explanation or evidence to support why the Examiner doubts the truth or accuracy of the inventors' disclosure been provided. In the absence of such an explanation or supporting evidence, the PTO's initial burden is not met and a lack of enablement rejection cannot be made. The Office action appears to be improperly shifting the burden upon applicants to provide experimental evidence of making and using the solvates. But this burden is misplaced in the absence of the PTO meeting its initial burden. Applicants urge for this additional reason, that the rejection for lack of enablement should be withdrawn at least for this reason.

For the above reasons, it is urged that the specification provides an adequate disclosure or how to make and use the claimed invention. Thus, the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement should be withdrawn.

**The Rejection under 35 U.S.C. §102**

The rejection of claims 1-6 and 9 under 35 U.S.C. §102(e), as being anticipated by Linker (DE 10219435), is respectfully traversed.

A German patent publication cannot be prior art under 35 U.S.C. §102(e). In fact, when considering applicants claim to priority, the DE publication is not prior art under any aspect of 35 U.S.C. §102. For the PTO to verify perfection of applicants' claim to priority, attached herewith are verified English language translations of German Application (DE) No. 10320784.8 filed on May 9, 2003, German Application (DE) No. 10336183.9 filed on August 7, 2003, German Application (DE) No. 10 2004 004142.3 filed on January 28, 2004, and PCT/EP2004/004455 filed on April 28, 2004. Applicants submit that the documents support that the instant claims are entitled to the earliest of these dates (May 9, 2003) as their priority date. The Linker (DE 10219435) reference was published on November 13, 2003, after this priority date. Thus, Linker is not available as 35 U.S.C. §102 prior art and the rejection should be withdrawn.

Applicants note that the Linker (DE 10219435) reference is indicated by the INPADOC system to correspond to the US application published as US Pub. No. 2005/0209251, published September 22, 2005. However, this reference also does not have an effective prior art date under 35 U.S.C. §102 prior to the claimed. This US application is a National stage of a PCT application that was not published in English. Thus, it does not have a 102(e) effective date.

**The Rejection under 35 U.S.C. §103**

The rejection of claims 1-4 and 7 under 35 U.S.C. §103 as being obvious over Cheng (J.Org.Chem., 1958) is respectfully traversed.

Cheng discloses a synthesis method for the eventual preparation of – what they call in the reference – 6-alkylpyrazolo-[3,4-d]pyrimidines. The compounds that Cheng calls 6-alkylpyrazolo-[3,4-d]pyrimidines are the compounds of the formula XV which have an amino group at the 4-position. See the formula XV in the diagram on page 193. It is evident that Cheng uses the 6-alkylpyrazolo-[3,4-d]pyrimidine term to refer to these compounds in distinction to Cheng's compounds of formula VI because Cheng uses the distinct term 6-alkyl-4-hydroxy-pyrazolo-[3,4-d]pyrimidine for these compounds. Hence, the discussion of any possible physiological activity at page 193, bottom left-side column, in Cheng refers to the compounds of formula XV not the compounds of formula VI in Cheng. Note that in this paragraph the only specific compound mentioned as having an activity is a 4-dimethylamino substituted compound.

As noted in the Office action, Cheng discloses 6-alkyl-4-hydroxy-pyrazolo-[3,4-d]pyrimidine compounds in Table II which differ from applicants' compounds at least because either: 1) the R2 group of Cheng is methyl and not ethyl or higher, and/or 2) the R1 group of Cheng, when a phenyl group, is not substituted phenyl. In both cases, the closest compounds of Cheng could be considered as adjacent homologs. However, such structural similarity, alone, does not support a prima facie case for obviousness. Particularly, in the case where the reference discloses no utility for the compounds that require modification or discloses such compounds only as intermediates, there is no basis to make even a small structural change to the compounds. See, e.g., In re Lalu, 74 F.2d 703, 223 USPQ 1257 (Fed. Cir. 1984), establishing that no motivation exists to modify compounds, which are taught only as intermediates, to arrive at compounds having a utility other than as an intermediate. See also, In re Stemniski, 170 USPQ 343 (CCPA 1971), finding that where a reference discloses no utility for compounds disclosed therein, the reference provides no motivation to one of ordinary skill in the art to modify such compounds even to compounds which are allegedly structurally similar. As the court rhetorically asked in Stemniski, at 347:

> "Where the prior art reference neither discloses nor suggests a utility for certain described compounds, why should it be said that a reference makes obvious to one of ordinary skill in the art an isomer, homolog or analog of related structure, when that

mythical, but intensely practical, person knows of no 'practical' reason to make the reference compounds, much less any structurally related compounds?"

In the instant case, Cheng is primarily directed to a synthesis method to provide compounds. Cheng provides only a brief and abstract discussion of possible activity of compounds in the paragraph at page 193, bottom left-side column. This discussion does not set forth any actual utility for the compounds discussed there. In any event, it should be clear that – even if this discussion did adequately describe a utility – it does not pertain to the compounds disclosed in Cheng which are most similar to the claimed compounds. There is no basis to tie this discussion in Cheng with the 6-alkyl-4-hydroxy-pyrazolo-[3,4-d]pyrimidine compounds disclosed in Cheng's formula VI and Table II. To the contrary, the only compound which Cheng identifies as having some activity (i.e., for inhibiting Neurospora crassa) is a compound having a 4-amino group like those described in Cheng's formula XV and Table III.

For the above reasons, it is urged that the record fails to provide a sufficient reason for one of ordinary skill in the art to modify the Cheng compounds in the manner necessary to arrive at the claimed invention. The 6-alkyl-4-hydroxy-pyrazolo-[3,4-d]pyrimidine compounds of Cheng, particulary the 17$^{th}$ and 19$^{th}$ species listed in Table II on page 195, are not disclosed for having any utility, except as intermediates. Thus, there is no reason for one of ordinary skill in the art to make even minor modifications to them.

Accordingly, it is urged that the rejection under 35 U.S.C. §103 should be withdrawn.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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